The Gene for Bazex-Dupré-Christol Syndrome Maps to Chromosome Xq

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Bazex-Dupré-Christol syndrome is an inherited condition with skin cancer predisposition characterized by follicular atrophoderma, hypotrichosis, and early onset of multiple basal cell carcinomas. Previous reports suggested an X-linked mode of inheritance. We therefore performed linkage analysis with microsatellite markers of the X chromosome in three families. We obtained evidence for X-linkage and regional assignment to Xq24–q27 of this syndrome (maximal lod score = 5.26 with a recombination fraction of 0% at the DXS1192 locus). This represents a first step towards the identification of a gene involved in hair follicle development and skin tumor formation. ***Key words: follicular atrophoderma/basal cell carcinoma/hypotrichosis/linkage analysis. J Invest Dermatol 105:87–91, 1995***

Bazex-Dupré-Christol syndrome, also known as Bazex syndrome [*Online Mendelian Inheritance in Man* (OMIM™) [1] 301845], is a rare genodermatosis with cancer predisposition. It was first described in 1964 as a combination of follicular atrophoderma, hypotrichosis, hypohidrosis, and multiple basal cell carcinomas with early onset [1–3]. Additional findings were subsequently reported, including milia, facial hyperpigmentation, and hair shaft dystrophy that revealed twisted, flattened shafts on electron microscopy. Systemic manifestations are absent.

Bazex syndrome is inherited as a Mendelian single-gene dominant trait. Although autosomal inheritance was hypothesized from the initial reports [3], an X-linked mode of inheritance was suggested by Viksnins and Berlin [4]. Indeed, this is supported by several lines of evidence. First, no instance of male-to-male transmission has been documented in published familial cases, with the exception of one pedigree described by Le Coulant *et al* [5], in which the affected status of a male was erroneous. Second, almost all of the daughters of affected fathers are affected. Finally, clinical observations of gender differences in disease expression are consistent with the Lyonization phenomenon [6].

Diagnosis of this syndrome is sometimes difficult. Multiple basal cell carcinomas also occur in nevoid basal cell carcinoma syndrome (NBCCS) (OMIM™ 109400), but in Bazex syndrome pits of the palms and soles, as well as skeletal abnormalities, are absent. NBCCS, on the other hand, does not feature hypotrichosis or hypohidrosis; and in addition, it is clearly an autosomal dominant disorder that maps to chromosome 9 in 9q22.3–q31 [7–10]. Follicular atrophoderma appears as funnel-shaped follicular depressions on the face and dorsa of the hands and resembles multiple ice pick marks. It is a fairly specific sign of Bazex syndrome, because these lesions are seen in only one other inherited condition, X-linked dominant chondrodysplasia punctata [11] (Happle type, OMIM™ 302960). There is clinical overlap between Bazex and Rombo syndromes [12] (OMIM™ 180730). Rombo syndrome is probably an autosomal dominant disorder and features vermiculate atrophoderma, basal cell carcinomas (BCCs), trichoepitheliomas, and acrocyanosis. Other conditions have been described by Parrish *et al* [13] (OMIM™ 146530) and Oley *et al* [14] (OMIM™ 109390), which although lacking follicular atrophoderma share several features with Bazex syndrome. These include hypotrichosis, milia, and possibly BCCs. The pedigrees described by these authors are consistent with either autosomal or X-linked dominant inheritance, because of the absence of male-to-male transmission. Therefore, it has been suggested that they may represent, along with Bazex syndrome, variations along the clinical expression spectrum of the same hereditary disorder [15,16].

The primary defect in Bazex syndrome is unknown. As a first step in our efforts to identify the causative gene, we performed genetic linkage studies with highly polymorphic markers of the X chromosome. Our results provide evidence that the gene for Bazex syndrome maps to the distal part of the long arm of chromosome X, in the Xq24–q27.1 region.

MATERIALS AND METHODS

Family Studies Seventeen affected individuals and eighteen unaffected relatives from three families were studied **(Fig 1)**. Four diagnostic criteria were considered: follicular atrophoderma, hypotrichosis, milia and BCCs. Hypotrichosis and milia are usually present during infancy and childhood but often improve with age. In each family studied, all four criteria were fulfilled. No single feature was present in every affected family member;

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Abbreviations: BCC, basal cell carcinoma; CA, cytosine-adenine; CEPH, Centre d'Études du Polymorphisme Humain; NBCCS, nevoid basal cell carcinoma syndrome; OMIM™, *Online Mendelian Inheritance in Man*.

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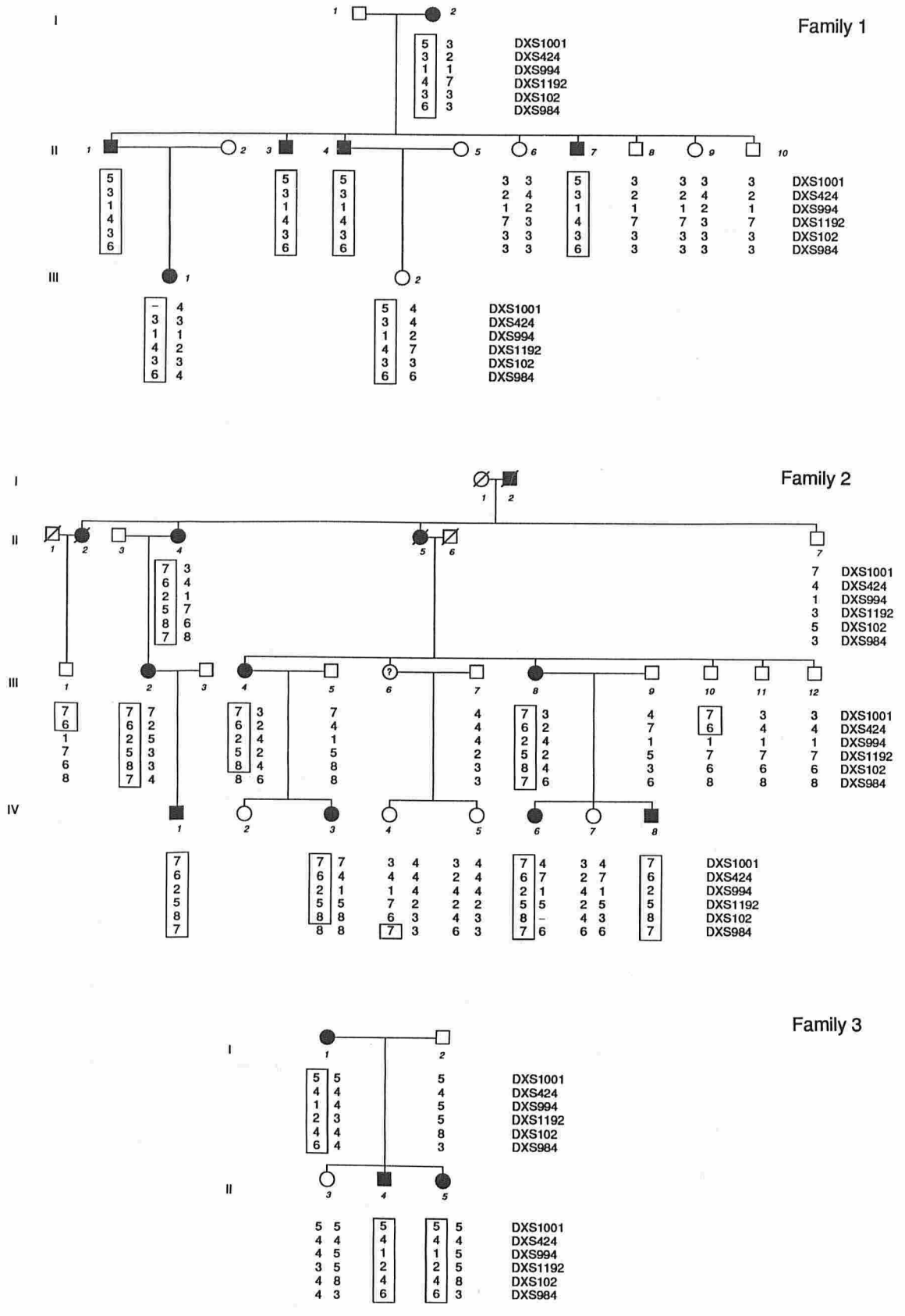

Figure 1. Analysis of haplotypes and recombination events in the three pedigrees define a genetic localization between DXS424 and DXS984. All members whose haplotype is shown underwent clinical examination and DNA analysis. Family 1 was not informative at loci DXS994 and DXS102. Family 3 was not informative at loci DXS1001, DXS424 and DXS102. Haplotypes were constructed based on the order of loci presented in **Table II**. *Boxed* haplotypes cosegregate with the disease. ?, phenotype unknown; —, allele mutation.

Table I. Diagnostic Features Were Determined on Clinical Examination in Each Family Studied

	Family 1	Family 2	Family 3
Number of affected members examined	6	8	3
Follicular atrophoderma	6	3	2
Basal cell carcinomas[a]	4	2	1
Hypotrichosis or hair dystrophy	5	8	3
Milia	6	7	3
Hypohidrosis	6	?	3
Maximal lod scores (DXS1192)[b]	2.02 (θ = 0%)	2.98 (θ = 0%)	0.56 (θ = 0%)

[a] Histologic diagnosis.
[b] Lod scores independently observed in each family.

however, at least two criteria were met, except for individual II-4 in family 2, who only exhibited hypotrichosis at age 73 **(Table I)**.

Clinical findings in the two French families are described in earlier reports [16,17]. Family 1 was evaluated at Rangueil Hospital, Toulouse, France. This is the family originally described by Bazex *et al* in 1964, now a three-generation family because of additional affected individuals. In this family, most BCCs had appeared before age 30. Family 2 was evaluated at Pellegrin-Enfants Hospital, Bordeaux, France. Because several affected family members displayed only hypotrichosis and milia, the entities described by Oley *et al* and Parrish *et al* were also considered as possible diagnoses [16]. This family was, in fact, the one previously described by Le Coulant *et al* [5] and Caubet [18], in which individual II-7, who had not been previously examined, was determined to be unaffected. This additional information ruled out male-to-male transmission. Another individual in this family (III-6) was unavailable for clinical examination and was considered unknown for linkage studies. BCCs were present only in patients III-2 and III-4 and had appeared between ages 40 and 50. Family 3 was evaluated at Jefferson Medical College, Philadelphia in 1991. Some members of this family were described previously by Viksnins and Berlin in 1977 [4]. In this family of Irish ancestry, differential diagnosis with Rombo syndrome was considered because of a questionable history of trichoepitheliomas in patient I-1. Biopsy reports were obtained subsequently and indicated that the benign facial lesions removed from this patient were not trichoepitheliomas. BCCs had appeared before age 30. Indeed, this family met all the criteria for Bazex syndrome. Other family members had been examined but were unavailable for linkage analysis. Several had basal cell carcinomas but are not included herein.¶

DNA Analysis Genomic DNA was extracted from blood leukocytes according to standard laboratory protocol. All individuals were genotyped by polymerase chain reaction (PCR) analysis using hypervariable microsatellite markers [19–22] Initially, microsatellite chromosome X markers were chosen at loci DXS1224, DXS1226, DXS992, DXS1068, DXS993, DXS1003, and DXS1039 from telomere to centromere on the short arm, and DXS441, DXS1106, DXS1001, DXS1047, DXS1227, DXS998, and DXS1193 from centromere to telomere on the long arm. Microsatellite markers were then studied at loci DXS1206, DXS424, DXS994, DXS1062, DXS1192, DXS102, DXS1232, and DXS984 (centromere to telomere) for refinement of the genetic map. Polymerase chain reaction (PCR) amplifications were performed in a total volume of 25 μl, containing 40 ng of genomic DNA, 50 nmol each primer, 2 mM dNTPs, and 0.3 units of Taq polymerase in 10 mM Tris HCl, pH 9, 50 mM KCl, 1.5 mM $MgCl_2$, 0.1% Triton X 100, and 0.01% gelatin. Amplification conditions were initial denaturation 96°C for 10 min, 30 cycles at 96°C for 40 seconds, 55°C for 30 seconds, 72°C for 40 seconds, and a final extension of 10 min at 72°C. An aliquot of each amplification product was run on a 6% polyacrylamide denaturing gel (urea 6 M), blotted onto nylon membrane, and hybridized with a $(CA)_{12}$ ^{32}P-labeled probe for 1 to 3 h. Membranes were washed 10 min at room temperature in 2 × saline sodium citrate (SSC), 0.1% sodium dodecyl sulfate (SDS) and autoradiographed. DNA of individual 134702 from the Centre d'Études du Polymorphisme Humain (CEPH) was included in each experiment as a control of allele size. Mendelian segregation was observed for all the markers except with loci DXS1001 in family 1 where a mutation of the paternal allele had occurred for individual III-1 (−2bp) and DXS102 in family 2 where a mutation of the paternal allele (+4bp) had occurred for individual IV-6. The calculated mutation rate in the family sample presented here (1.75×10^{-3}) is consistent with the 0.1% observed in more extensive microsatellite typing studies [19].

Linkage Analysis Pairwise and multipoint analyses were performed using the MLINK and LINKMAP options of the LINKAGE 5.1 program [23,24]. Calculations were made assuming a rare X-linked dominant trait (gene frequency = 10^{-6}) with a penetrance of 0.9 in heterozygous female and 1 in male subjects (estimated from the sample studied). The markers were ordered according to the map established at the Fifth International X Chromosome Workshop, Heidelberg [25]. Genetic distances calculated from the CEPH family panel were used [19]. Allele numbers and frequencies were obtained from the Genome Interactive Databases [26].

RESULTS

Families were initially genotyped using 14 evenly distributed markers on the X chromosome. This initial study excluded linkage with Xp, centromeric and telomeric regions of Xq, the lod scores being <-2 at a recombination fraction (θ) of 10% for loci DXS1224, DXS1226, DXS992, DXS1068, DXS993, DXS1003, DXS1039, DXS441, DXS1106, DXS998, and DXS1193. The first significant positive lod scores were obtained at loci DXS1001, DXS1047, and DXS1227. Eight additional markers were tested to further refine the linkage map **(Table II)**. The highest pairwise lod score (Z_{max}) was obtained with marker DXS1192 (Z_{max} = 5.26 at θ = 0% for the whole family set). Separate linkage analysis of each family at locus DXS1192 yielded significant maximal lod scores in family 1 (Z_{max} = 2.02 at θ = 0%) and family 2 (Z_{max} = 2.98 at θ = 0%).

No recombinants were seen in either family with markers DXS994, DXS1047, DXS1062, DXS1192, DXS102, and DXS1232. Recombination events in family 2 with locus DXS424 (for individuals III-1 and III-10) and DXS984 (for individuals III-4 and IV-4) defined the proximal and distal boundaries of the Bazex

¶ Rabinowitz L, Williams L, Kline T, Anderson C, Fretzin D, Esterly N: Rombo syndrome vs. Bazex syndrome (abstr). *Pediatr Dermatol* 9:223, 1992.

Table II. Significant Pairwise lod Scores Are Observed Between the Bazex Locus and Different Markers of the Xq24–q27.1 Region (Ordered Centromere to Telomere)

	Recombination Fractions								
Locus	0.00	0.01	0.05	0.10	0.20	0.30	0.40	Z_{max}	θ_{max}
DXS1212	$-\infty$	*−0.41*	*0.76*	*1.07*	*1.04*	*0.12*	*0.30*	*1.11*	*0.14*
DXS1001	$-\infty$	2.19	2.59	2.50	1.96	1.23	0.47	2.59	0.06
DXS424	$-\infty$	1.91	2.50	2.57	2.24	1.61	0.79	2.57	0.09
DXS994	4.20	4.13	3.85	3.49	2.70	1.85	0.91	4.20	0.00
DXS1047	4.82	4.74	4.41	3.98	3.05	2.02	0.91	4.82	0.00
DXS1062	3.98	3.90	3.55	3.10	2.12	1.06	0.11	3.98	0.00
DXS1192	5.26	5.17	4.79	4.29	3.21	2.02	0.77	5.26	0.00
DXS102	2.98	2.93	2.72	2.44	1.85	1.19	0.46	2.98	0.00
DXS1232	3.28	3.23	3.02	2.74	2.13	1.43	0.66	3.28	0.00
DXS984	$-\infty$	2.84	3.34	3.29	2.67	1.76	0.72	3.36	0.06
DXS1227	$-\infty$	0.30	1.00	1.19	1.11	0.78	0.35	1.21	0.13

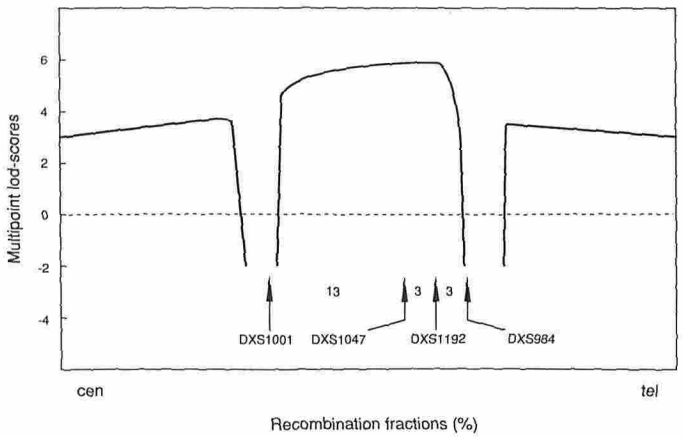

Figure 2. Maximal multipoint lod scores are observed at locus DXS1192. Multipoint analysis was performed in the three families versus the four most informative microsatellite markers of Xq24–q27. Recombination fractions (indicated in %) represent a genetic distance of 21 cM according to Haldane's mapping function. Lod scores are indicated as $\log_{10}$. cen, centromeric region; tel, telomeric region.

locus **(Fig 1)**. No haplotype was consistently shared by probands of each family **(Fig 1)**. Alleles present on Bazex chromosomes at loci DXS1047, DXS1062, DXS1192, DXS1062, and DXS102 differed in each family. A common allele was found on Bazex chromosomes at DXS1232 in all three families, but a significant difference versus non-Bazex chromosomes could not be shown due to the small size of our family sample.

Multipoint analysis was performed with the most informative markers. The maximum likelihood estimate for the location of the Bazex gene was at locus DXS1192 (multipoint lod score = 5.88), with boundaries in accordance with the haplotype analysis **(Fig 2)**. These results support genetic localization of the Bazex locus within a 21 centimorgan (cM) interval on the distal part of Xq, as the genetic distance between DXS1001 and DXS984 is approximately the same as between DXS424 and DXS984.

DISCUSSION

We present evidence for X-linkage of Bazex syndrome. Incomplete penetrance was observed in family 1 where the daughter (III-2), aged 18, of an affected father (II-4) was unaffected. Paternity was confirmed by genotyping. In family 2, individual III-6, whose phenotype was unknown, is likely to be unaffected as she shares her putative maternal haplotype with her three unaffected brothers. In addition, her two unaffected daughters, from whom her genotype was deduced, inherited two different maternal haplotypes **(Fig 1)**. Interval boundaries primarily depend on the unaffected status of several members of family 2, specifically III-1, III-10, and IV-4. Although incomplete penetrance cannot be excluded, it appears unlikely for III-10 because he is the father of an unaffected female [16] (not shown here). Affected status with incomplete penetrance for IV-4 would yield a much narrower genetic interval for Bazex locus (between DXS102 and DXS984). As family 2 was uninformative at locus DXS1232, no further evidence for this alternative interval could be obtained. Although no linkage disequilibrium was found, a common ancestry for the French families who originated from the southwest of France cannot be excluded.

Although the entire family set was small due to the rarity of this disorder, linkage analysis performed in each family yielded maximal lod scores over 2.0, which is considered significant for X chromosome [27], in families 1 and 2. Family 3 was not large enough to show significant lod scores, nevertheless the positive lod scores ($Z_{max} = 0.56$ at $\theta = 0$) observed at loci DXS1212, DXS994, DXS1206, DXS1047, DXS1062, DXS1192, and DXS984 support the localization found in the other families. These results are consistent with genetic homogeneity, despite slight clinical interfamilial differences (specifically lower incidence and later onset of BCCs in family 2).

No other cutaneous disorder, to our knowledge, maps to the Xq24–q27.1 region. In X-linked dominant chondrodysplasia punctata, which also features follicular atrophoderma, linkage analysis excluded the Xq24–q27 region [28]. Another disorder of the hair follicle, keratosis follicularis spinulosa decalvans, which is transmitted as an X-linked recessive trait with partial expression in some female carriers [29], maps to Xpter [30]. Hence neither of these X-linked skin conditions is allelic with Bazex syndrome. Hereditary conditions described by Parrish *et al* and Oley *et al* may represent phenotypical variations of Bazex syndrome, because of clinical similarities and putative X-linked inheritance. Therefore linkage with Xq24–q27 markers should be tested in these families. In Rombo syndrome, because of male-to-male transmission in the original pedigree [12], it is possible that another gene is located on an autosome, resulting in a close or identical phenotype.

Hair follicle stem cells are likely to play a role in non-melanoma skin cancer development [31]. The identification of the gene involved in Bazex syndrome may yield important information about the relationship between hair-follicle development and skin carcinogenesis. Therefore, a search for candidate genes present in this region led us to consider the *UBE2A* gene, which maps to Xq24–q25 [32], as a potential candidate. This is a ubiquitin-conjugating enzyme of which the yeast homolog *RAD6* is involved in ultraviolet-induced DNA damage repair. Actually, the human *UBE2A* gene functionally complements the DNA repair deficient *rad6* yeast strain [33]. Other human homologs of DNA repair *RAD* yeast genes are involved in xeroderma pigmentosum, another syndrome with skin cancer predisposition, and trichothiodystrophy, another hair disorder [34]. Furthermore, reduced DNA repair capacities have been reported in patients with early-onset basal cell carcinomas and a family history of basal cell carcinomas [35]. We do not yet know whether DNA repair is deficient or not in the Bazex syndrome. Therefore results of DNA repair studies and molecular analysis of the *UBE2A* gene would be of great interest.

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